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10/087,473	03/01/2002	Melissa K. Carpenter	090/003C	1663

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EXAMINER	
TON, THAIAN N	

ART UNIT	PAPER NUMBER
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/087,473	CARPENTER ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) *21 and 22* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *01 March 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/25/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-22 are pending and under current examination.

Election/Restrictions

Applicant's election with traverse of claims 1-20 (Group I) in the Paper filed 4/2/2004 is acknowledged. The traversal is on the ground(s) that the Office has not established that a serious burden would be imposed if the tree groups in the present application were examined together. This is not found persuasive because each of the methods in Groups II-III are materially different, require a different protocol and the inventions are have acquired a separate status in the art as shown by their different classification. Further, as stated in the Restriction Requirement, if Applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. See prior Office action, pp. 3-4.

The requirement is still deemed proper and is therefore made FINAL.

Claims 21 and 22 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected groups, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the paper filed 4/2/04.

Information Disclosure Statement

Applicant's IDS, filed 4/25/02 has been considered.

Double Patenting

A rejection based on double patenting of the "same invention" type finds its support in the language of 35 U.S.C. 101 which states that "whoever invents or discovers any new and useful process ... may obtain a patent therefor ..." (Emphasis added). Thus, the term "same invention," in this context, means an invention drawn to identical subject matter. See *Miller v. Eagle Mfg. Co.*, 151 U.S. 186 (1894); *In re Ockert*, 245 F.2d 467, 114 USPQ 330 (CCPA 1957); and *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970).

A statutory type (35 U.S.C. 101) double patenting rejection can be overcome by canceling or amending the conflicting claims so they are no longer coextensive in scope. The filing of a terminal disclaimer cannot overcome a double patenting rejection based upon 35 U.S.C. 101.

Claim 1 is provisionally rejected under 35 U.S.C. 101 as claiming the same invention as that of claim 11 of copending Application No. 10/039,956. This is a provisional double patenting rejection since the conflicting claims have not in fact been patented. Both sets of claims are directed to the same method for producing differentiated cells from a donor culture of undifferentiated pPS cells by preparing a suspension of pPS cells from an undifferentiated donor culture, replating and culturing the suspended cells on a surface so that they differentiate without forming embryoid bodies, and harvesting differentiated cells from the solid surface.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re*

Goodman, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 2-10, 19, 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 12-15 and 35 of copending Application No. 10/039,956. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are directed to the same methods of producing differentiated cells from a donor culture of undifferentiated pPS cells. The instant claims are directed to methods for producing differentiated cells from a donor culture of pPS cells by culturing the pPS cells on a solid surface in an environment essentially free of feeder cells, changing the medium used to culture the cells so that they differentiate, and harvesting the differentiated cells from the solid surface. The '956 claims are directed to methods of producing differentiated cells from a donor culture by changing the medium in which the cells are culture and harvesting the cells. Thus, the instant claims are made obvious by the '956 claims in that they recite method steps and particular factors in common.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1-5, 7, 8, 10-20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 23-31of copending Application No. 09/888,309. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are both directed to methods of producing neural cells from human embryonic stem cells. The instant claims are directed to methods for producing neural cells by differentiating pPS cells in the presence of a factor that promotes differentiation, such as BDNF or NT-3. The '309 claims are directed to methods for producing neural cells from human ES cells by culturing the ES cells in a medium that contains a neurotrophin, such as NT-3 or BDNF. Thus the instant claims are made obvious by the '309 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claims 1, 2, 7, 12-17, 19, 20 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 3, 4, 6-8, 12, 13 of copending Application No. 09/994,440. Although the conflicting claims are not identical, they are not patentably distinct from each other

because both sets of claims are directed to methods of differentiating undifferentiated ES cells (or pPS cells). The instant claims are directed to methods for producing neural cells by differentiating pPS cells on a solid surface in the presence of a factor that promotes differentiation. The '440 claims are directed to methods for generating differentiated cells by using passaged ES cells and differentiating the cells on a solid surface that promotes differentiation. Thus, the instant claims are made obvious by the '440 claims.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 4 is unclear. The claim recites that the donor culture is free of feeder cells, which are replated. It is unclear what "which" refers to. It is suggested that the claim be written to state that the donor culture is replated.

Claim 5 is unclear. The claim recites that the solid surface "bears" a polycation. "Bears" can mean to hold up, or to have a feature or characteristic of. The solid surface does not hold up or have a characteristic of a polycation, it contains or is coated with a polycation. Appropriate correction is required.

Claim 7 is unclear. The claim recites that the cells are cultured after replating in a medium containing a factor that promotes differentiation. The cells are not replated in a medium, but on a solid surface. It is suggested that the claim be written to state that after replating the cells are cultured in a medium containing a factor that promotes differentiation. Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 19 is rejected under 35 U.S.C. 102(b) as being anticipated by Bhatia *et al.* [**J. Exp. Med.**, 189(7):1139-1147 (April 1999)].

The claim is directed to a committed precursor cell prepared to the method according to claim 12. Note that this is a product-by-process claim.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product. See In re Ludtke, supra. Whether the rejection is based on "inherency" under 35 USC

102, on "prima facie obviousness" under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO's inability to manufacture products or to obtain and compare prior art products. In re Best, Bolton, and Shaw, 195 USPQ 430, 433 (CCPA 1977) citing In re Brown, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972). Further, see MPEP §2113, "Even though product-by process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process."

Bhatia teach human hematopoietic stem cells isolated from human cord blood. See Materials and Methods, p. 1140, 2nd column.

Accordingly, Bhatia teach the claimed invention.

Claims 19 and 20 are rejected under 35 U.S.C. 102(b) as being anticipated by Boss *et al.* [U.S. Pat. No., 5,411,883, published May 2, 1995].

The claims are directed to committed precursor cells and fully differentiated cells. Note that the claims are product-by-process claims, see *supra*.

Boss teach the isolation of neuron progenitor cells [see col. 6-8]. Boss teach the *in vitro* differentiation of the neuron progenitor cells to form neurons and glia [see col. 6, lines 4-12 and col. 19-20].

Accordingly, Boss anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson [**PNAS**, 92:7844-7848 (1995)] in view of Weiss [**U.S. Pat. No.** 5,851,832, published Dec. 22, 1998, Reference C of Applicants' IDS, filed 4/26/02].

The claims are directed to methods for producing differentiated cells from a donor culture of undifferentiated pPS cells by preparing a suspension of pPS cells from the undifferentiated donor culture, replating and culturing the suspended cells on a solid surface so that they differentiate without forming embryoid bodies, and harvesting differentiated cells from the solid surface.

Thomson teaches primate embryonic stem cells isolated from a rhesus monkey that are capable of differentiation to multiple cell types when cultured in the absence of fibroblasts [see p. 7845, 2nd column, 2nd ¶] and could differentiate to all three embryonic germ layers when injected into scid mice, generating, for example, neural tissue and ganglia [see p. 7846 2nd column, 1st ¶]. Thomson teaches that the ES cells were plated at low density in the absence of fibroblasts on gelatin-treated tissue culture plates in medium which contains 90% DMEM, 20% FBS, 1% nonessential amino acid stock and 1000 units of cloned human LIF. The ES cells then differentiated. See p. 7845, 1st column, *In Vitro Differentiation* and Figure 1. Note that the instant specification teaches that suspension of ES cells was preformed by dissociation of aggregates. See Example 2, p. 27. Thus, Thomson's teaching of dissociation of ES cells aggregates fulfills the claims' limitations for preparation of a suspension of pPS cells. Thomson does not teach the replating of the cells on a solid surface that is coated with a polycation, and harvesting differentiated cells from the solid surface, or culturing the ES cells in a medium containing a specific factor that promotes differentiation (for example, BDNF, NT-

3), or the generation of precursor cells committed to a restricted cell lineage, as required by the claims.

However, prior to the time the claimed invention was made, Weiss teach methods of *in vitro* proliferation and differentiation of neural stem cells. Weiss teach that stem cells give rise to progenitor cells which give rise to proliferating cells, such as neuroblasts, glioblasts, etc. See col. 1, lines 63-67. Weiss teach methods for the *in vitro* differentiation of neural stem cells and stem cell progeny by isolating stem cells from a mammal, exposing the cell to a medium containing a growth factor, inducing the cell(s) to proliferate and differentiate. Weis teach that in the presence of a proliferation-inducing growth factor, the stem cell divides and gives rise to a sphere of undifferentiated cells composed of stem cells or progenitor cells, and when these cells are dissociated and plated as single cells on a non-adhesive substrate and under conditions that allow differentiation, the cells differentiate into neurons, astrocytes and oligodendrocytes. See col. 11, lines 39-50. In particular, the dissociated neural cells can be induced to differentiate by culturing the cells on a substrate, such as poly-ornithine treated glass or plastic to differentiate into neurons and glial cells. See col. 18, lines 30-55. Furthermore, exogenous growth factors may be added to direct the differentiation of the stem cells, for example BDNF and neurotrophin 3. See col. 2, lines 25-39.

Accordingly, in view of the combined art of Thomson and Weiss, it would have been obvious for one of ordinary skill in the art to use the undifferentiated ES cells

taught by Thomson and direct differentiation into neural cells, by the methods taught by Weiss. One of ordinary skill would have been motivated to direct differentiation of undifferentiated cells to provide an unlimited source of neural cells, as supported by Weiss (see col. 10, lines 30-33).

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson [PNAS, 92:7844-7848 (1995)] in view of Weiss [U.S. Pat. No. 5,851,832, published Dec. 22, 1998, Reference C of Applicants' IDS, filed 4/26/02] as applied to claims 1-10, 12-20 above, and further in view of Melton *et al.* [U.S. Pat. No. , 6,686,198 B1, filed April 9, 1997].

The claim is directed to methods of obtaining differentiated cells from a donor culture of undifferentiated pPS cells comprising culturing the pPS cells on a solid surface in an environment essentially free of feeder cells, changing the medium used to culture the cells so that they differentiate before there is overgrowth or formation of colonies, wherein the medium contains noggin or follistatin, and harvesting differentiated cells from the solid surface.

Thomson teaches primate embryonic stem cells isolated from a rhesus monkey that are capable of differentiation to multiple cell types when cultured in the absence of fibroblasts [see p. 7845, 2nd column, 2nd ¶] and could differentiate to all three

embryonic germ layers when injected into scid mice, generating, for example, neural tissue and ganglia [see p. 7846 2nd column, 1st ¶]. Thomson teaches that the ES cells were plated at low density in the absence of fibroblasts on gelatin-treated tissue culture plates in medium which contains 90% DMEM, 20% FBS, 1% nonessential amino acid stock and 1000 units of cloned human LIF. The ES cells then differentiated. See p. 7845, 1st column, *In Vitro Differentiation* and Figure 1. Note that the instant specification teaches that suspension of ES cells was preformed by dissociation of aggregates. See Example 2, p. 27. Thus, Thomson's teaching of dissociation of ES cells aggregates fulfills the claims' limitations for preparation of a suspension of pPS cells. Thomson does not teach the replating of the cells on a solid surface that is coated with a polycation, and harvesting differentiated cells from the solid surface, or culturing the ES cells in a medium containing a specific factor that promotes differentiation (for example, BDNF, NT-3), or the generation of precursor cells committed to a restricted cell lineage, as required by the claims.

However, prior to the time the claimed invention was made, Weiss teach methods of *in vitro* proliferation and differentiation of neural stem cells. Weiss teach that stem cells give rise to progenitor cells which give rise to proliferating cells, such as neuroblasts, glioblasts, etc. See col. 1, lines 63-67. Weiss teach methods for the *in vitro* differentiation of neural stem cells and stem cell progeny by isolating stem cells from a mammal, exposing the cell to a medium containing a

growth factor, inducing the cell(s) to proliferate and differentiate. Weis teach that in the presence of a proliferation-inducing growth factor, the stem cell divides and gives rise to a sphere of undifferentiated cells composed of stem cells or progenitor cells, and when these cells are dissociated and plated as single cells on a non-adhesive substrate and under conditions that allow differentiation, the cells differentiate into neurons, astrocytes and oligodendrocytes. See col. 11, lines 39-50. In particular, the dissociated neural cells can be induced to differentiate by culturing the cells on a substrate, such as poly-ornithine treated glass or plastic to differentiate into neurons and glial cells. See col. 18, lines 30-55. Furthermore, exogenous growth factors may be added to direct the differentiation of the stem cells, for example BDNF and neurotrophin 3. See col. 2, lines 25-39.

Thomson and Weiss do not teach that the differentiation medium used to culture the cells contains noggin or follistatin. However, Melton teaches methods for inducing neuronal cell differentiation. Particularly, they teach that stem cells can be induced to differentiate into a committed progenitor cell, or a terminally differentiated neuronal cell by culturing with an agent that antagonizes the biological action of activin, such as follistatin, and a second agent which is a neurotrophic factor that enhances a particular differentaiton fate of the cell, such as noggin. See col. 9, lines 8-30 and col. 9-10, bridging ¶ and claims 1, 4 and 13.

Accordingly, in view of the combined teachings of Thomson, Weiss and Melton, it would have been obvious for one of ordinary skill in the art at the time

the claimed invention was made, to culture stem cells, such as those taught by Thomson to differentiate in a culture medium that contains follistatin or nogin, as taught by Weiss and Melton. One of ordinary skill in the art would have been motivated to do so because the presence of factors such as follistatin and noggin can be employed to maintain the integrity of a culture of terminally-differentiated neuronal cells by preventing loss of differentiation as taught by Melton [see col. 9, lines 8-13]

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

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